

CORRESPONDENCE

Open Access



Immune response to vaccination against SARS-CoV-2 in hematopoietic stem cell transplantation and CAR T-cell therapy recipients

Xi Wu¹, Lu Wang¹, Lu Shen¹, Lin He¹ and Kefu Tang^{2*}

Abstract

Recipients after hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor T-cell (CAR-T) therapy are at increased risk for unfavorable outcomes after SARS-CoV-2 infection. The efficacy of COVID-19 vaccines remains undetermined in this vulnerable population, we therefore conducted a pooled analysis to evaluate the immune response after vaccination. A total of 46 studies were finally included, comprising 4757 HSCT and 174 CAR-T recipients. Our results indicated that HSCT and CAR-T recipients had an attenuated immune response to SARS-CoV-2 vaccination compared with healthy individuals, while time interval between transplant and vaccination, immunosuppressive therapy (IST) and lymphocyte counts at vaccination significantly affected the humoral response in HSCT recipients. In addition, seroconversion was significantly higher in patients with BCMA-based CAR-T than those with CD19-based CAR-T. Thus, an adapted vaccination strategy for HSCT and CAR-T recipients may be required, and further research on the effect of a booster dose of COVID-19 vaccine and the role of cellular response after vaccination is warranted.

Keywords: Hematopoietic stem cell transplantation (HSCT), Chimeric antigen receptor T-cell (CAR-T) therapy, SARS-CoV-2 vaccination, Immune response

To the Editor,

The pandemic caused by SARS-CoV-2 has led to global mortality of over 6 million deaths and vaccination is the primary strategy to stop this public health emergency. Recipients after hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor T-cell (CAR-T) therapy are at increased risk for severe COVID-19 and unfavorable outcomes [1]. Previous studies showed

blunted humoral responses to vaccination against SARS-CoV-2 among HSCT and CAR-T recipients [2–6]. With emerging evidence available, we performed a comprehensive meta-analysis to evaluate the immune responses to COVID-19 vaccines in recipients of HSCT and CAR-T (Additional file 1: Methods S1 and Additional file 1: Fig. S1).

Overall, 44 studies comprising 4757 HSCT patients [1182 of autologous HSCT (autoHSCT), 3495 of allogeneic HSCT (alloHSCT), 80 of autoHSCT or alloHSCT (mixed)] (Additional file 1: Table S1) and 12 studies comprising 174 CAR-T recipients were included (Additional file 1: Table S2). For HSCT, five studies investigated the response after partial vaccination, 38 studies evaluated the response after completed vaccination, and seven

*Correspondence: fish_tang@hotmail.com

² Prenatal Diagnosis Center, Department of Clinical Laboratory, Changning Maternity and Infant Health Hospital, East China Normal University, Shanghai 200051, China
Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

studies assessed the response after a third dose. As for CAR-T, 11 studies evaluated the response after completed vaccination, and one study assessed the response following a third dose.

The seropositive rates of the second and third dose were significantly higher than the first dose, while no significant difference in seroconversion between the second and third dose (Fig. 1A). The pooled humoral response rate was 81.4% following completed vaccination in HSCT patients (Additional file 1: Fig. S2), with response rates of 86.1% and 79.6% for autoHSCT and alloHSCT. The response rates after one and three vaccine doses were 40.8% and 78.6%, respectively

(Additional file 1: Figs. S3–S4). Although pooled analysis could not be performed due to heterogeneity of data, significantly lower antibody titres were observed in HSCT patients compared with healthy controls (Additional file 1: Table S3).

Our results indicated response rate significantly increased with the time interval from HSCT to vaccination: 38.2% within 6 months, 62.3% between 6 and 12 months, and 87.9% after 12 months (Fig. 1B and Additional file 1: Fig. S5). Among autoHSCT recipients, stratified analysis by underlying diseases demonstrated myeloma patients had a marginal increased

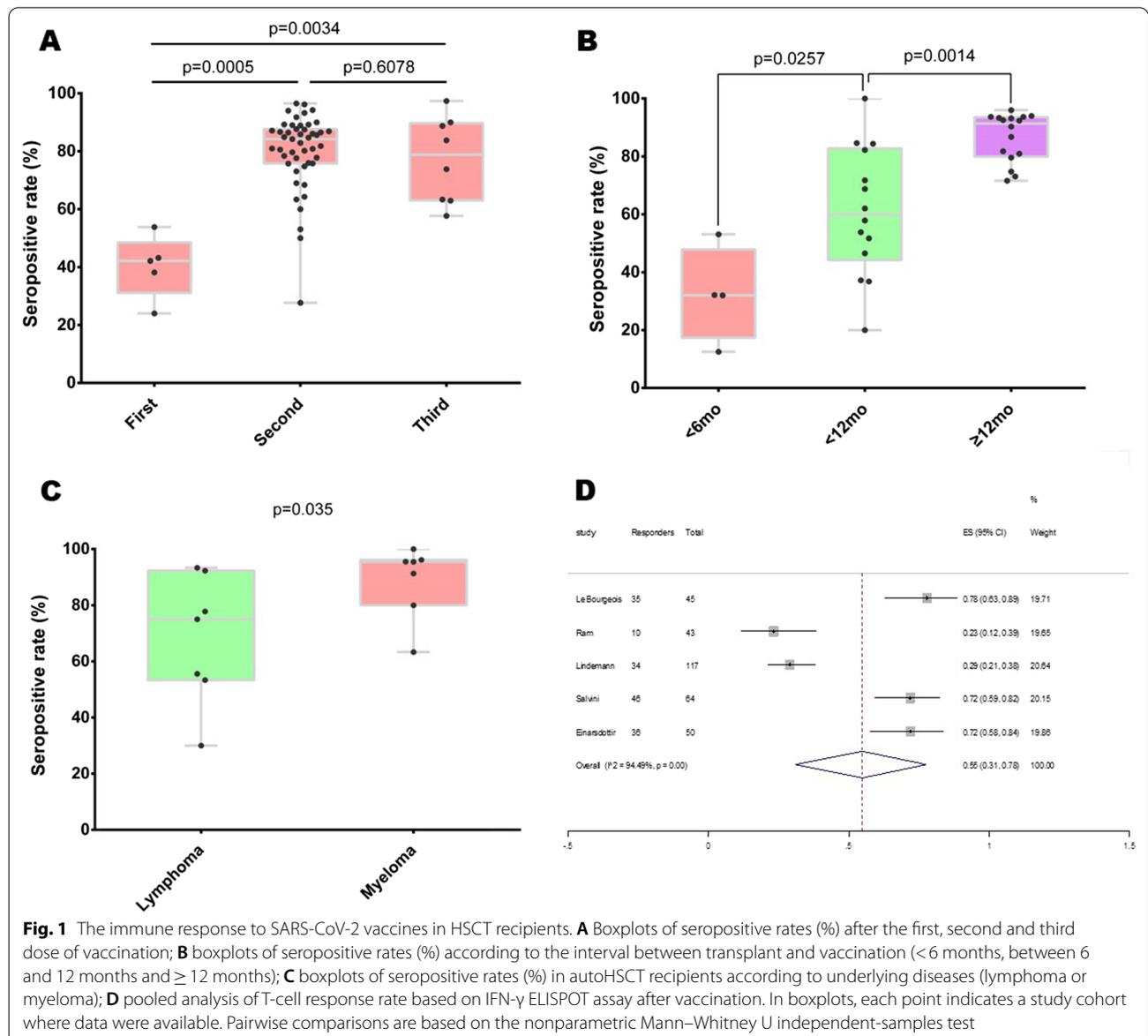


Fig. 1 The immune response to SARS-CoV-2 vaccines in HSCT recipients. **A** Boxplots of seropositive rates (%) after the first, second and third dose of vaccination; **B** boxplots of seropositive rates (%) according to the interval between transplant and vaccination (< 6 months, between 6 and 12 months and ≥ 12 months); **C** boxplots of seropositive rates (%) in autoHSCT recipients according to underlying diseases (lymphoma or myeloma); **D** pooled analysis of T-cell response rate based on IFN-γ ELISPOT assay after vaccination. In boxplots, each point indicates a study cohort where data were available. Pairwise comparisons are based on the nonparametric Mann–Whitney U independent-samples test

seroconversion rate compared to lymphoma patients ($P=0.035$, Fig. 1C).

In addition, immunosuppressive therapy (IST: OR=5.86, 95% CI: 3.74–9.18, $P<10^{-5}$; Additional file 1: Fig. S6) and lymphopenia (lymphocyte counts<1G/L among alloHSCT: OR=4.44, 95% CI: 2.56–7.70, $P<10^{-5}$; Additional file 1: Fig. S7) at vaccination were significantly associated with seronegative response. And neither the status of graft-versus-host disease (GVHD) (Additional file 1: Fig. S8) nor age (Additional file 1: Fig. S9) was significantly associated with seroconversion after vaccination. Furthermore, T-cell response rate based on IFN- γ ELISPOT assay was 55% in HSCT patients (Fig. 1D).

As for CAR-T recipients, the combined serological response rate after SARS-CoV-2 vaccination was 35.9% (Fig. 2A). When stratified by different constructs, seroconversion was significantly higher in patients with BCMA-based CAR-T than those with CD19-based CAR-T (Fig. 2B).

Our analysis demonstrated suboptimal immune responses to SARS-CoV-2 vaccination in patients after HSCT and CAR-T, especially for CD19-based CAR-T recipients. Although we found no significant difference between the second and third dose, the boost vaccination against SARS-CoV-2 was identified to improve humoral response in HSCT patients initially

seronegative following the second dose [7, 8]. Moreover, antibody levels were reported to significantly increase after the third dose, counteracting the waning immunity after completed vaccination [9, 10]. Of note, new evidence illustrated a majority of alloHSCT patients without GVHD produced neutralizing antibody against Delta and Omicron variants after a third dose [11], underscoring the benefits of a booster dose. Additionally, we found HSCT patients vaccinated after recent transplantation, on IST or with lymphopenia were at higher risk of insufficient responses to COVID-19 vaccines, indicating the importance of immune recovery status for SARS-CoV-2 vaccination.

Interestingly, seroconversion rate was significantly higher in patients with BCMA-based CAR-T compared to those with CD19-directed CAR-T. But due to sparse data, more studies are needed to validate our result and further investigate the impact of different CAR-T constructs on serological response after SARS-CoV-2 vaccination.

In summary, our study indicated that HSCT and CAR-T recipients developed impaired immune responses to COVID-19 vaccines. Thus, an adapted vaccination strategy for these patients may be required. Moreover, the effect of a booster dose and the role of cellular response after SARS-CoV-2 vaccination in

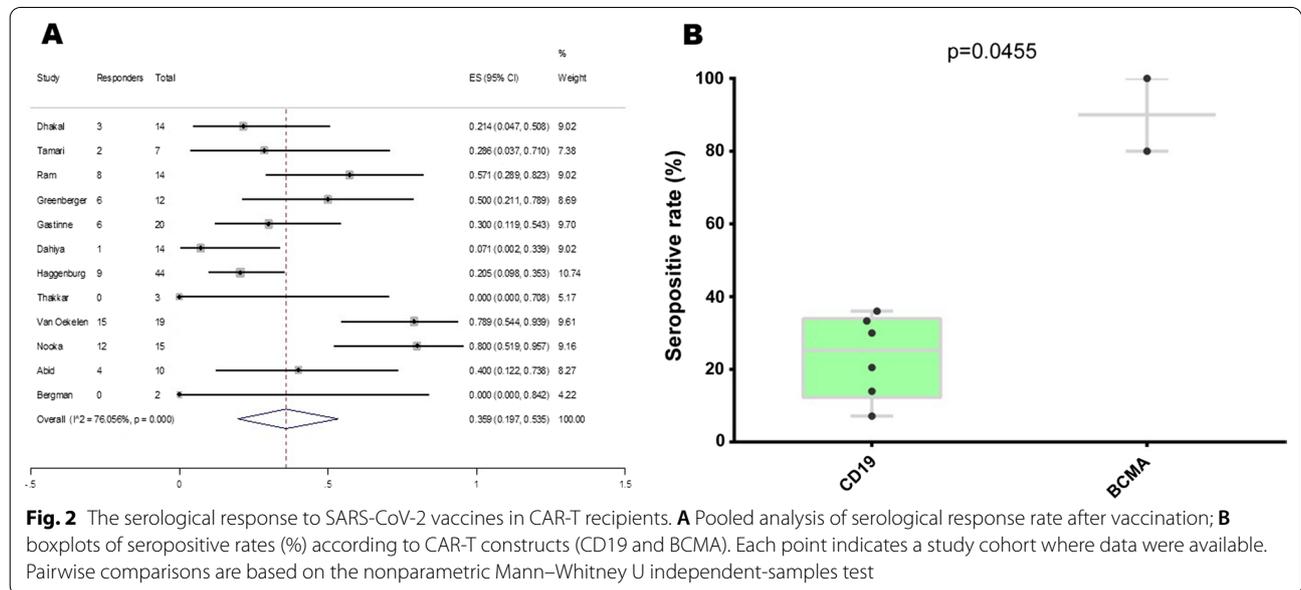


Fig. 2 The serological response to SARS-CoV-2 vaccines in CAR-T recipients. **A** Pooled analysis of serological response rate after vaccination; **B** boxplots of seropositive rates (%) according to CAR-T constructs (CD19 and BCMA). Each point indicates a study cohort where data were available. Pairwise comparisons are based on the nonparametric Mann–Whitney U independent-samples test

HSCT and CAR-T recipients should be addressed in future research.

Abbreviations

HSCT: Hematopoietic stem cell transplantation; CAR-T: Chimeric antigen receptor T-cell; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; autoHSCT: Autologous HSCT; alloHSCT: Allogeneic HSCT; IFN- γ : Interferon-gamma; ELISPOT: Enzyme-linked immunosorbent spot; IST: Immunosuppressive therapy; OR: Odds ratio; CIs: Confidence intervals; GVHD: Graft-versus-host disease.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13045-022-01300-9>.

Additional file 1: Methods S1. **Supplementary Figure S1.** Flowchart of study selection. **Supplementary Figure S2.** Forest plots for the pooled analysis of serological response after completed vaccination in HSCT recipients. **Supplementary Figure S3.** Forest plots for the pooled analysis of serological response after one dose of vaccination in HSCT recipients. **Supplementary Figure S4.** Forest plots for the pooled analysis of serological response after three doses of vaccination in HSCT recipients. **Supplementary Figure S5.** Forest plots for the pooled analysis of serological response according to the interval between transplant and vaccination (<6 months, between 6-12 months and \geq 12 months). **Supplementary Figure S6.** Forest plots for the association of immunosuppressive therapy and the risk of seronegative response after COVID-19 vaccination in HSCT recipients. **Supplementary Figure S7.** Forest plots for the association of lymphopenia and the risk of seronegative response after COVID-19 vaccination in alloHSCT recipients. **Supplementary Figure S8.** Forest plots for the association of the status of GVHD and the risk of seronegative response after COVID-19 vaccination in HSCT recipients. **Supplementary Figure S9.** Forest plots for the association of age and the risk of seronegative response after COVID-19 vaccination in HSCT recipients. **Supplementary Table S1.** Study characteristics for HSCT. **Supplementary Table S2.** Study characteristics for CAR-T. **Supplementary Table S3.** Anti-Spike (S) SARS-CoV-2 antibody titres in HSCT patients vs. healthy controls.

Acknowledgements

Not applicable.

Author contributions

Concept and design: XW, KFT; acquisition and interpretation of data: LW, LS, KFT, XW; drafting of the manuscript: KFT, XW; critical revision of the manuscript: KFT, XW, LH. All authors read and approved the final manuscript.

Funding

This work was supported by grant from the Research Start-up Fund in Changning Maternity and Infant Health Hospital (2021Y-15).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Bio-X Institutes, Key Laboratory for the Genetics of Developmental and Neuropsychiatric Disorders (Ministry of Education), Shanghai Jiao Tong University, Shanghai 200030, China. ²Prenatal Diagnosis Center, Department of Clinical Laboratory, Changning Maternity and Infant Health Hospital, East China Normal University, Shanghai 200051, China.

Received: 14 May 2022 Accepted: 3 June 2022

Published online: 16 June 2022

References

- Ljungman P, de la Camara R, Mikulska M, Tridello G, Aguado B, Zahrani MA, Apperley J, Berceanu A, Bofarull RM, Calbacho M, Ciceri F, Lopez-Corral L, Crippa C, Fox ML, Grassi A, Jimenez MJ, Demir SK, Kwon M, Llamas CV, Lorenzo JLL, Mielke S, Orchard K, Porras RP, Vallisa D, Xhaard A, Knelange NS, Cedillo A, Kröger N, Piñana JL, Styczynski J. COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey. *Leukemia*. 2021;35(10):2885–94. <https://doi.org/10.1038/s41375-021-01302-5>.
- Dhakal B, Abedin S, Fenske T, Chhabra S, Ledebner N, Hari P, Hamadani M. Response to SARS-CoV-2 vaccination in patients after hematopoietic cell transplantation and CAR T-cell therapy. *Blood*. 2021;138(14):1278–81. <https://doi.org/10.1182/blood.2021012769>.
- Maneikis K, Šablauskas K, Ringelevičiūtė U, Vaitekėnaitė V, Čekauskienė R, Kryžauskaitė L, Naumovas D, Banys V, Pečeliūnas V, Beinortas T, Griškevičius L. Immunogenicity of the BNT162b2 COVID-19 mRNA vaccine and early clinical outcomes in patients with haematological malignancies in Lithuania: a national prospective cohort study. *Lancet Haematol*. 2021;8(8):e583–92. [https://doi.org/10.1016/S2352-3026\(21\)00169-1](https://doi.org/10.1016/S2352-3026(21)00169-1).
- Ram R, Hagin D, Kikozashvili N, Freund T, Amit O, Bar-On Y, Beyar-Katz O, Shefer G, Moshiaishvili MM, Karni C, Gold R, Kay S, Glait-Santar C, Eshel R, Perry C, Avivi I, Apel A, Benyamini N, Shasha D, Ben-Ami R. Safety and immunogenicity of the BNT162b2 mRNA COVID-19 vaccine in patients after allogeneic HCT or CD19-based CART therapy—a single-center prospective cohort study. *Transplant Cell Ther*. 2021;27(9):788–94. <https://doi.org/10.1016/j.jtct.2021.06.024>.
- Redjoul R, Le Bouter A, Parinet V, Fourati S, Maury S. Antibody response after third BNT162b2 dose in recipients of allogeneic HSCT. *Lancet Haematol*. 2021;8(10):e681–3. [https://doi.org/10.1016/S2352-3026\(21\)00274-X](https://doi.org/10.1016/S2352-3026(21)00274-X).
- Abid MA, Abid MB. SARS-CoV-2 vaccine response in CART-cell therapy recipients: a systematic review and preliminary observations. *Hematol Oncol*. 2022;40(2):287–91. <https://doi.org/10.1002/hon.2957>.
- Abid MB, Rubin M, Ledebner N, Szabo A, Longo W, Mohan M, Shah NN, Fenske TS, Abedin S, Runaas L, D'Souza A, Chhabra S, Dhakal B, Hamadani M. Efficacy of a third SARS-CoV-2 mRNA vaccine dose among hematopoietic cell transplantation, CAR T cell, and BiTE recipients. *Cancer Cell*. 2022;40(4):340–2. <https://doi.org/10.1016/j.ccell.2022.02.010>.
- Maillard A, Redjoul R, Klemencie M, Labussière Wallet H, Le Bourgeois A, D'Aveni M, Huynh A, Berceanu A, Marchand T, Chantepie S, Botella Garcia C, Loschi M, Joris M, Castilla-Llorente C, Thiebaut-Bertrand A, François S, Leclerc M, Chevallier P, Nguyen S. Antibody response after 2 and 3 doses of SARS-CoV-2 mRNA vaccine in allogeneic hematopoietic cell transplant recipients. *Blood*. 2022;139(1):134–7. <https://doi.org/10.1182/blood.202104232>.
- Debie Y, Vandamme T, Goossens ME, van Dam PA, Peeters M. Antibody titres before and after a third dose of the SARS-CoV-2 BNT162b2 vaccine in patients with cancer. *Eur J Cancer*. 2022;163:177–9. <https://doi.org/10.1016/j.ejca.2021.12.025>.
- Huang A, Cicin-Sain C, Pascin C, Epp S, Audigé A, Müller NJ, Nilsson J, Bankova A, Wolfensberger N, Vilinovsky O, Nair G, Hockl P, Schanz U, Kouyos RD, Hasse B, Zinkernagel AS, Trkola A, Manz MG, Abela IA, Müller AMS. Antibody response to SARS-CoV-2 vaccination in patients following allogeneic hematopoietic cell transplantation. *Transplant Cell Ther*. 2022;28(4):214.e1–214.e11. <https://doi.org/10.1016/j.jtct.2022.01.019>.
- Canti L, Ariën KK, Desombere I, Humblet-Baron S, Pannus P, Heyndrickx L, Henry A, Servais S, Willems E, Ehx G, Goriely S, Seidel L, Michiels J, Willems B, Goossens ME, Beguin Y, Marchant A, Baron F. Antibody

response against SARS-CoV-2 Delta and Omicron variants after third-dose BNT162b2 vaccination in allo-HCT recipients. *Cancer Cell*. 2022;40(4):335–7. <https://doi.org/10.1016/j.ccell.2022.02.005>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

